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Sodium Bicarbonate for Severe Metabolic Acidemia and Acute Kidney Injury
The BICARICU-2 Randomized Clinical Trial

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IMPORTANCE The effect of sodium bicarbonate infusion on outcome in patients with severe metabolic acidemia and moderate to severe acute kidney injury is unknown.

OBJECTIVE To determine whether sodium bicarbonate infusion is associated with day 90 all-cause mortality in patients with severe metabolic acidemia and moderate to severe acute kidney injury.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label, clinical trial conducted with 640 patients in 43 French intensive care units from October 6, 2019, to December 19, 2023, with 90-day follow-up. The last date of follow-up was June 17, 2024. Adults with severe metabolic acidemia (defined as pH ≤7.20) and moderate to severe acute kidney injury were enrolled.

INTERVENTION Patients were randomized 1:1 to receive either intravenous sodium bicarbonate infusion or no sodium bicarbonate to target an arterial pH of 7.30 or higher.

MAIN OUTCOMES AND MEASURES The primary outcome was day 90 all-cause mortality. Secondary outcomes included day 28 and day 180 all-cause mortality; use of organ support therapy, vasopressors, or invasive mechanical ventilation; intensive care unit and hospital length of stay; intensive care unit–acquired infections; fluid balance; day-7 Sequential [Sepsis-related] Organ Failure Assessment score (6 organ systems' function is evaluated and scored from 0 [no dysfunction] to 4 [failure]; total score ranges from 0 [normal] to 24 [maximum failure]); and major adverse kidney events on day 90.

RESULTS Among 640 randomly assigned patients, 627 were analyzed (313 in the control group and 314 in the bicarbonate group). The median age was 67 years (IQR, 59-74 years); 194 of 314 patients (62%) in the bicarbonate group and 185 of 313 controls (59%) were male. In the primary analysis, day 90 all-cause mortality was 195 of 314 patients (62.1%) in the bicarbonate group and 193 of 313 (61.7%) in the control group (absolute difference, 0.4; 95% CI, −7.2 to 8.0; P = .91). There was no evidence of a group effect on day 28 or day 180 all-cause mortality. Among 18 secondary outcomes, kidney replacement therapy was used in 109 of 314 (35%) bicarbonate group patients and 157 of 313 (50%) controls (absolute difference, −15.5; 95% CI, −23.1 to −7.8). No evidence of a group effect was found on other secondary outcomes, including adverse events.

CONCLUSIONS AND RELEVANCE For patients with severe metabolic acidemia and moderate to severe acute kidney injury, intravenous sodium bicarbonate did not affect mortality.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04010630

Visual Abstract
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Supplemental content

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JAMA. doi:10.1001/jama.2025.20231
Published online October 29, 2025.

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Reported consequences of severe metabolic acidemia (pH ≤7.20)[1-4] include impaired cardiac contractility, arrhythmias, pulmonary vasoconstriction, systemic vasodilation, altered kidney blood flow, cerebral edema, and diaphragmatic dysfunction, which adversely affect patient outcomes.[4,5] Hyperchloremic acidosis, lactate accumulation, and endogenous anion accumulation during acute kidney injury (AKI) are the most common causes of metabolic acidemia in critically ill patients.[2,6] The administration of intravenous sodium bicarbonate to manage severe metabolic acidemia with or without AKI remains controversial.[1,4,7-10]

The randomized multicenter clinical trial BICARICU-1 compared the infusion of 4.2% intravenous sodium bicarbonate with no sodium bicarbonate in unselected critically ill patients with severe metabolic acidemia.[3] The primary outcome of day 28 mortality, organ failure on day 7, or both did not differ significantly between the groups. However, a preplanned analysis of the randomization stratum of patients with moderate to severe AKI showed a day 28 mortality of 63% in the control group and a day 28 mortality of 46% in the bicarbonate group.[3,11] Moreover, in this stratum, kidney replacement therapy (KRT) was received by 73% of controls and 51% of bicarbonate group patients.

Subsequent observational studies suggested benefits of sodium bicarbonate infusion for patients with severe acidemia and severe AKI, very severe metabolic acidemia (pH <7.15)[12,13] or older than 60 years, sepsis, and moderate acidemia.[14] A target trial emulation conducted with 6157 patients suggested an association between sodium bicarbonate administration and reduced 30-day mortality.[15] Furthermore, studies on the timing of KRT initiation have shown that, in most cases, delaying KRT for critically ill patients is safe and may be associated with fewer adverse events than early initiation.[16-19] Some evidence suggests that sodium bicarbonate administration for patients with acidemia may be used as a temporizing measure to delay KRT initiation.[3]

We hypothesized that, for critically ill patients with moderate to severe AKI and severe metabolic acidemia, infusion of sodium bicarbonate would improve outcomes.

This randomized clinical trial aimed to assess whether sodium bicarbonate infusion improved day 90 all-cause mortality for critically ill patients with both severe metabolic acidemia and moderate to severe AKI.

Key Points

Question For patients with severe metabolic acidosis and moderate to severe acute kidney injury, does sodium bicarbonate infusion decrease day 90 all-cause mortality?

Findings In this multicenter randomized clinical trial that included 640 patients, sodium bicarbonate infusion was not associated with lower day 90 all-cause mortality (195 of 314 patients in the bicarbonate group and 193 of 313 patients in the control group).

Meaning Sodium bicarbonate infusion does not improve day 90 all-cause mortality.

Methods

This second trial of sodium bicarbonate in the intensive care unit (ICU; BICARICU-2) was an open-label, investigator-initiated, multicenter randomized clinical trial with 2 parallel groups. The study protocol and statistical analysis plan were approved by the Comité de Protection des Personnes Nord Ouest 1 in accordance with French law and the Declaration of Helsinki.[20] The ClinicalTrials.gov identification is NCT04010630. The protocol has been published and its report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and checklist.[21]

Informed written consent from the patient or a relative was obtained at enrollment when possible. When a patient was too ill to make decisions and had no relatives available to provide consent, the emergency procedure set forth in French law was applied (eAppendix in Supplement 1).

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Patient Eligibility Criteria

The patients were enrolled at 43 ICUs in France between October 6, 2019, and December 19, 2023. The last date of follow-up was June 17, 2024.

Patients older than 18 years were eligible if they had a total Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score greater than 4 or an arterial lactate concentration greater than or equal to 2 mmol/L within 48 hours after ICU admission and if the following criteria were met within 6 hours before enrollment: pH 7.20 or less, serum bicarbonate level 20 mEq/L or less, $PaCO_2$ 45 mm Hg or less, and moderate to severe AKI, defined as stage 2 or 3 in the Kidney Disease Improving Global Outcomes classification (eTable 1 in Supplement 1).[3,21]

We did not include patients with any of the following: respiratory acidosis ($PaCO_2$ higher than 45 mm Hg while breathing spontaneously), proven bicarbonate wasting via the gastrointestinal tract (volume higher than 1500 mL/24 h) or urinary tract, baseline glomerular filtration rate 10 mL/min or less, ketoacidosis, sodium bicarbonate infusion, KRT within 24 hours before screening or planned for the next 6 hours, exogenous acid poisoning (metformin, salicylate, methanol, or ethylene glycol), pregnancy or breastfeeding, or life expectancy fewer than 48 hours.[3,21] Patients who were enrolled in another study, in the exclusion period after enrollment in another study, under guardianship, or employed by the sponsor or main investigator were not included. In accordance with French law, we did not include patients who were not covered by the French statutory health care insurance system.

Randomization

Within 48 hours after ICU admission, eligible patients were randomly assigned to receive either 4.2% sodium bicarbonate infusion (bicarbonate group) or no sodium bicarbonate infusion (control group). Randomization was centrally performed using a computer-generated allocation sequence. Stratification was performed at the trial center according to age (<65 years vs ≥65 years) and pH (<7.10 vs 7.11-7.20), balanced

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with a 1:1 ratio by minimization. At each center, the trial investigator accessed the randomization tool with an identifier and a password.

Intervention

The intervention was intravenous administration of 4.2% sodium bicarbonate, targeting an arterial pH of 7.30 or higher throughout the next 28 days or until ICU discharge (eFigure 1 in Supplement 1). Each infusion consisted of 125 to 250 mL within 30 minutes, with a maximum of 1000 mL within 24 hours after enrollment and blood gas analysis 1 to 4 hours after the end of each infusion.[3] Controls did not receive sodium bicarbonate infusions or placebo. The indications for KRT were standardized in both groups. Immediate KRT initiation was recommended at any time for patients whose serum potassium level exceeded 6.5 mEq/L with electrocardiogram changes typical of hyperkalemia, who had cardiogenic pulmonary edema with no urine output and a ratio of Pao_2 to fraction of inspired oxygen lower than 200 mm Hg while receiving fraction of inspired oxygen above 50% and a positive end-expiratory pressure above 5 cm H_2O, or both. Kidney replacement therapy was also recommended for patients meeting at least 2 of the following criteria 24 hours after enrollment: urine output less than 0.3 mL/kg/h during 24 hours, pH 7.20 or less despite resuscitation,[9] and serum potassium level greater than 6.5 mEq/L.

Outcomes

The primary outcome was day 90 all-cause mortality.

Secondary outcomes were day 28 and day 180 all-cause mortality; use of KRT, vasopressors, or invasive mechanical ventilation; ICU and hospital length of stay; fluid balance; day 7 SOFA score; ICU-acquired infections; and major adverse kidney events on day 90.[22] The use of KRT was defined as any day the patient received KRT.[3,16,18,23] The use of vasopressors was defined as any day the patient was treated with vasopressors.[3,16,18,23] Adverse events were also recorded. All outcomes were collected by the site investigators.

Statistical Analysis

The statistical analysis plan has been published (the final protocol can be found in Supplement 2, the statistical analysis plan is listed in Supplement 3, and the statistical analysis plan and protocols changes are in Supplement 4).[21] In the BICARICU-1 trial,[3] day 90 all-cause mortality in the stratum with moderate to severe AKI was 64% with sodium bicarbonate therapy and 81% without it.[5] To obtain 80% power to detect a 10% absolute decrease in day 90 all-cause mortality (from 80% to 70%, with a conservative assumption) with sodium bicarbonate therapy, 588 patients were needed, with the 2-sided α risk set at .05 (overall *P* value for the trial) and a *P* value threshold of .001 for the 2 interim analyses (Haybittle-Peto boundary). We assumed that less than 8% of the patients would have unevaluable data and therefore planned to include 640 patients (320 in each group).

We performed analyses on 2 distinct populations. First, analyses were conducted for the primary population, excluding only patients who withdrew consent or were found after randomization to be under guardianship or not covered by the French health care insurance system. Second, a per-protocol analysis was conducted, in which patients who received sodium bicarbonate were compared with patients who did not receive sodium bicarbonate regardless of their initial randomization group and regardless of timing of administration. Patients with protocol deviations related to eligibility criteria were excluded from this analysis.

The primary analysis of day 90 all-cause mortality (primary outcome) in the 2 groups was evaluated with the χ^2 test, with the results reported as absolute frequency differences and 95% CIs.

The group effect on the primary outcome was also evaluated using a logistic model with and without adjustment on randomization strata (center, pH, and age) and Elixhauser score. The results are reported as odds ratios with their 95% CIs. On these analyses, the center effect was checked with a mixed-effect model, considering the center as a random and then a fixed variable. To assess the robustness of the primary outcome analysis and to account for any postrandomization bias because nonadherence to the protocol might have been nonrandom, we conducted a post hoc inverse probability weighting analysis.[24] A bootstrap estimator was then used to calculate robust odds ratios of treatment effects with their 95% CIs.

Cumulative mortality was estimated with the Kaplan-Meier method and compared between groups with the log-rank test. Hazard ratios for death and their 95% CIs were calculated with Cox proportional hazards regression.

In addition, subgroup analyses were performed. The primary outcome was studied according to randomization strata (pH and age), preplanned subgroups (sepsis and median SOFA score), and post hoc subgroups (kidney SOFA score, serum lactate level, type of admission, cardiac arrest, hemorrhagic shock, and center). The results are reported in a forest plot as odds ratios with their 95% CIs. Continuous variables were dichotomized by the median. The statistical analysis plan did not include a provision that subgroup analyses would be corrected for multiple comparisons. Therefore, *P* values are not displayed, and these results should be interpreted with caution. We also performed a post hoc exploratory analysis focusing on the main types of metabolic acidemia.[25]

Secondary outcomes were evaluated using the absolute frequency differences or the median difference (estimated by the Hodges-Lehmann method) with 95% CIs. To describe the biology parameters over time, a mixed-regression model was used, including the patient as a random variable.

The tests for all outcomes were 2 sided and statistical significance was set at .05. For multiplicity of testing, the CIs were not adjusted, and the intervals should therefore not be used instead of hypothesis testing.

An independent data and safety monitoring board blinded to group allocation supervised the study and reviewed the safety data (eAppendix in Supplement 1). Interim analyses were performed after enrollment of 200 and 400 of the 640 planned patients.

All analyses were performed with SAS version 9.2 (SAS Institute) or R version 4.4.0 (R Foundation for Statistical Computing). The interim analysis was conducted on February 8, 2021, and August 16, 2022. The final analysis was started on July 24, 2024, and the post hoc analysis was conducted after peer review on March 2, 2025.

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Figure 1. Patient Flowchart

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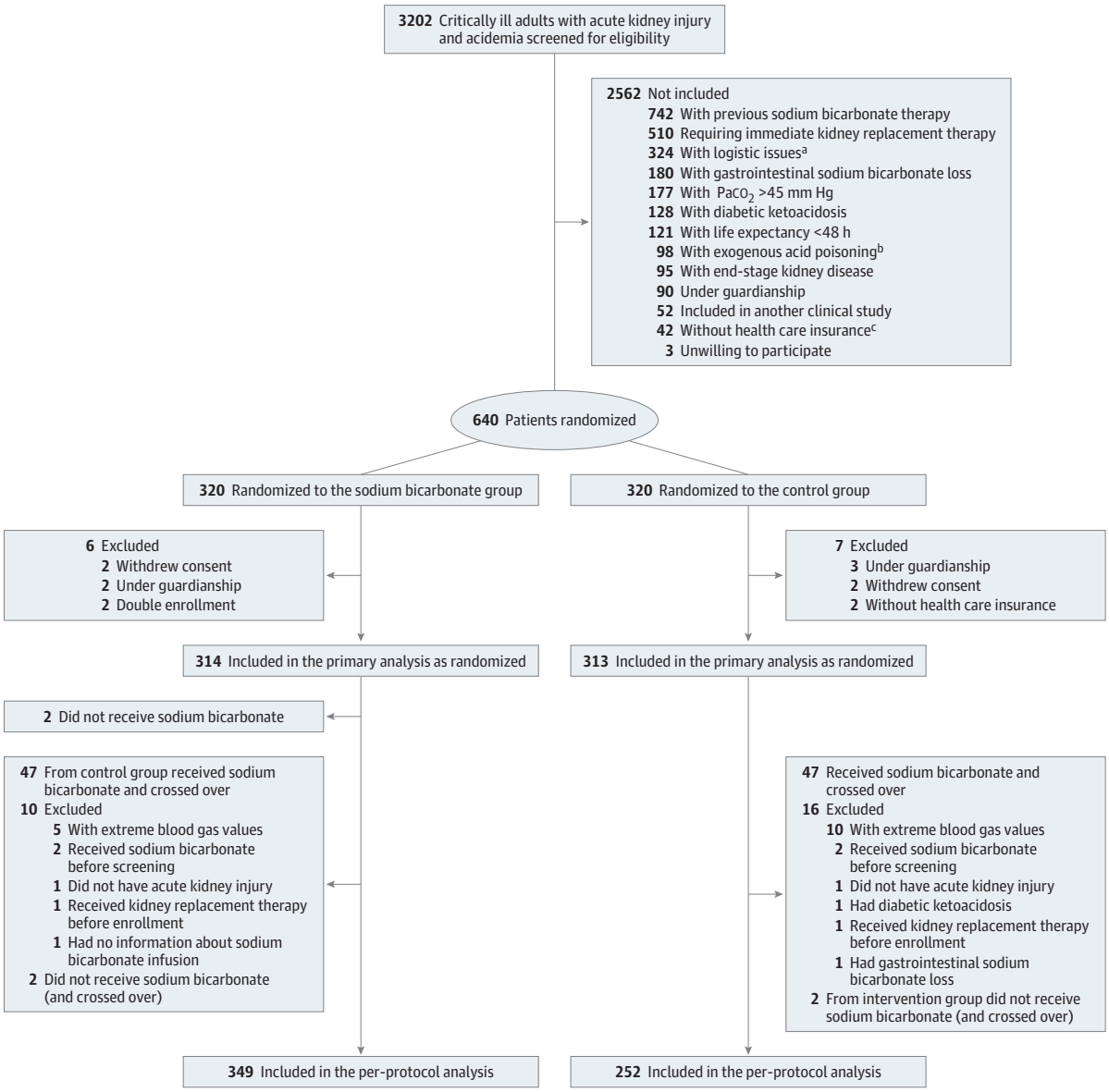
3202 Critically ill adults with acute kidney injury and acidemia screened for eligibility
2562 Not included
742 With previous sodium bicarbonate therapy
510 Requiring immediate kidney replacement therapy
324 With logistic issues[a]
180 With gastrointestinal sodium bicarbonate loss
177 With PaCO2 >45 mm Hg
128 With diabetic ketoacidosis
121 With life expectancy <48 h
98 With exogenous acid poisoning[b]
95 With end-stage kidney disease
90 Under guardianship
52 Included in another clinical study
42 Without health care insurance[c]
3 Unwilling to participate
640 Patients randomized
320 Randomized to the sodium bicarbonate group
320 Randomized to the control group
6 Excluded
2 Withdrew consent
2 Under guardianship
2 Double enrollment
7 Excluded
3 Under guardianship
2 Withdrew consent
2 Without health care insurance
314 Included in the primary analysis as randomized
313 Included in the primary analysis as randomized
2 Did not receive sodium bicarbonate
47 From control group received sodium bicarbonate and crossed over
10 Excluded
5 With extreme blood gas values
2 Received sodium bicarbonate before screening
1 Did not have acute kidney injury
1 Received kidney replacement therapy before enrollment
1 Had no information about sodium bicarbonate infusion
2 Did not receive sodium bicarbonate (and crossed over)
47 Received sodium bicarbonate and crossed over
16 Excluded
10 With extreme blood gas values
2 Received sodium bicarbonate before screening
1 Did not have acute kidney injury
1 Had diabetic ketoacidosis
1 Received kidney replacement therapy before enrollment
1 Had gastrointestinal sodium bicarbonate loss
2 From intervention group did not receive sodium bicarbonate (and crossed over)
349 Included in the per-protocol analysis
252 Included in the per-protocol analysis

Stratification was performed at the trial center according to age (<65 years vs ≥65 years) and pH (<7.10 vs 7.11-7.20), balanced with a 1:1 ratio by minimization. Five patients in the sodium bicarbonate group and 10 patients in the control group were enrolled with a pH greater than 7.24, a serum bicarbonate level greater than 20 mEq/L, or $Paco_2$ greater than 47 mm Hg. These 15 patients were considered outliers and were excluded from the primary analysis. One patient in the sodium bicarbonate group and 1 patient in the control group did not reach Kidney Disease Improving Global Outcomes stage 2 or 3 acute kidney injury and were excluded from the primary analysis.

[a]Logistic issues: eligible patients unable to be enrolled due to logistic constraints such as unavailability of research personnel or insufficient time.

[b]Exogenous acid poisoning: metformin, salicylate, methanol, or ethylene glycol.

[c]According to French law, having valid health insurance is mandatory to participate in any research program.

Results

Patients

Figure 1 shows the flowchart for the 640 patients in the study. Recruitment occurred from October 6, 2019, to December 19, 2023, and stopped when the planned sample size was achieved. Among randomly assigned patients, median age was 67 years (IQR, 59-74 years). Data on race and ethnicity were not collected because it is unlawful in France unless specifically mentioned and authorized by the institutional review board. A total of 194 of 314 patients (62%) in the bicarbonate group and 185 of 313 controls (59%) were male; 120 patients (38%) in the bicarbonate group and 128 controls (41%) were female. For the primary outcome, day 90 follow-up data were available for all patients. The primary

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Table 1. Baseline Characteristics of the Patients

Characteristics	Group	
	Bicarbonate (n = 314)	Control (n = 313)
Age, median (IQR), y	67 (59-74)	67 (58-74)
Age ≥65 y, No. (%)	182 (58)	183 (58)
Male, No. (%)	194 (62)	185 (59)
Female, No. (%)	120 (38)	128 (41)
Body mass index, median (IQR)	27 (24-31) [n = 309]	27 (23-31) [n = 302]
SAPS II at enrollment, median (IQR)[a]	61 (52-75) [n = 313]	61 (50-76) [n = 312]
Comorbidities, No. (%)		
Chronic hypertension	159 (51)	168 (54)
Alcohol misuse	87 (28)	85 (27)
Diabetes mellitus	86 (27)	89 (28)
Currently smokes	76 (24)	82 (26)
Immunodeficiency[b]	53 (17)	76 (24)
Cirrhosis of the liver	47 (15)	57 (18)
Coronary artery disease	44 (14)	46 (15)
Chronic kidney disease	41 (13)	49 (16)
Severe liver failure	27 (9)	20 (6)
Chronic obstructive pulmonary disease	27 (9)	41 (13)
Chronic heart failure	9 (3)	25 (8)
Chronic respiratory failure	7 (2)	15 (5)
Modified Elixhauser Comorbidity Index score, median (IQR)[c]	0 (0-8)	3 (0-10)
McCabe score, No. (%)[d]		
0	172/279 (62)	151/277 (55)
1	84/279 (30)	84/277 (30)
2	23/279 (8)	42/277 (15)
Type of admission, No. (%)		
Medical	214 (68)	216 (69)
Surgical	100 (32)	97 (31)
Main cause of acidemia at enrollment, No. (%)[e]		
Septic shock	172 (55)	166 (53)
Hemorrhagic shock	44 (14)	45 (14)
Acute kidney injury	25 (8)	25 (8)
Cardiac arrest	20 (6)	18 (6)
Acute on chronic liver failure	7 (2)	9 (3)
Other	46 (15)	50 (16)
SOFA score at enrollment, median (IQR)[f]		
Cardiovascular	4 (3-4)	4 (3-4)
Respiratory	2 (1-3)	2 (1-3)
Kidney	2 (1-3)	2 (1-3) [n = 312]
Neurologic	1 (0-2) [n = 311]	1 (0-3) [n = 307]
Hepatic	0 (0-2) [n = 311]	0 (0-2) [n = 310]
Hematologic	0 (0-1) [n = 313]	0 (0-2) [n = 309]
Total	10 (8-13) [n = 308]	11 (8-13) [n = 302]
Kidney SOFA score ≤2, No. (%)	200 (64)	187 (60)
Blood pressure, median (IQR), mm Hg		
Systolic	107 (94-121) [n = 310]	109 (95-122) [n = 311]
Diastolic	56 (49-63) [n = 310]	56 (49-63) [n = 311]
Mean[g]	72 (65-79) [n = 309]	72 (66-80) [n = 311]
Invasive mechanical ventilation, No. (%)	241 (77)	231 (74)
Vasopressor support, No. (%)	252/311 (81)	246/312 (79)

(continued)

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Table 1. Baseline Characteristics of the Patients (continued)

Characteristics	Group	
	Bicarbonate (n = 314)	Control (n = 313)
Laboratory test results, median (IQR)[h]		
Arterial pH	7.15 (7.08-7.18)	7.15 (7.09-7.19)
Pao_2/Fio_2, mm Hg	232 (140-335) [n = 308]	227 (158-352) [n = 308]
$Paco_2$, mm Hg	37 (31-42)	37 (30-42)
Serum bicarbonate, mEq/L	13 (10-15) [n = 313]	12 (10-15) [n = 311]
Serum lactate, mmol/L	5.9 (3.0-10.8) [n = 297]	5.7 (2.4-10.4) [n = 291]
Serum lactate >2 mmol/L, No. (%)	245/297 (82)	230/291 (79)
Serum sodium, mEq/L	136 (133-141) [n = 309]	136 (132-140) [n = 304]
Serum potassium, mEq/L	4.8 (4.1-5.5) [n = 309]	4.6 (4.0-5.5) [n = 304]
Serum chloride, mEq/L	105 (100-110) [n = 306]	105 (99-110) [n = 296]
Serum calcium, mg/dL	7.9 (7.3-8.6) [n = 224]	7.9 (7.3-8.4) [n = 232]
Serum ionized calcium, mg/dL	4.3 (4.1-4.6) [n = 237]	4.4 (4.1-4.7) [n = 247]
Serum albumin, g/dL	2.4 (2.1-2.9) [n = 189]	2.5 (2.1-3.0) [n = 189]
Serum creatinine, mg/dL	2.2 (1.5-3.2) [n = 305]	2.3 (1.6-3.3) [n = 298]
Blood urea nitrogen, mg/dL	42 (28-64) [n = 298]	42 (25-67) [n = 292]

Abbreviations: Fio_2, fraction of inspired oxygen; SAPS II, Simplified Acute Physiology Score version II; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.

SI conversion factors: To convert serum bicarbonate to mmol/L, multiply by 1.0; to convert serum sodium to mmol/L, multiply by 1.0; to convert serum potassium to mmol/L, multiply by 1.0; to convert serum chloride to mmol/L, multiply by 1.0; to convert serum calcium or ionized calcium to mmol/L, multiply by 0.25; to convert serum albumin to g/L, multiply by 10; to convert creatinine to μmol/L, multiply by 88.4; to convert blood urea nitrogen to mmol/L, multiply by 0.357. Body mass index is calculated as weight in kilograms divided by height in meters squared.

[a] The SAPS[26] is based on 17 variables and ranges from 0 to 163, with higher values indicating greater disease severity.

[b] Defined as any of the following: steroid treatment with prednisone-equivalent dose higher than prednisone at 1 mg/kg/d for 30 days or more, HIV infection, biotherapy, and chemotherapy.

[c] A modified Elixhauser Comorbidity Index score was computed with a subset of available comorbidities and the van Walraven weighting system.[27] The following conditions were included: alcohol misuse, drug or tobacco use, diabetes, hypertension, congestive heart failure, kidney failure, liver disease (acute or chronic), chronic pulmonary disease (including chronic obstructive pulmonary disease), and immunosuppression. Each condition was assigned a weight according to the van Walraven scheme, and the conditions were summed to generate a composite comorbidity score. Comorbidities were identified from prospectively collected clinical data.

[d] The McCabe score ranges from 0 to 2, with higher scores indicating greater severity of comorbidities.

[e] Other causes of metabolic acidosis are listed in eTable 11 in Supplement 1.

[f] The SOFA score[28] is computed as the sum of 6 subscores (cardiovascular, respiratory, neurologic, kidney, hepatic, and hematologic), each of which can range from 0 to 4; the total score can thus range from 0 to 24, with higher values indicating greater severity of organ failure.

[g] Mean blood pressure conveys 1/3 systolic blood pressure + 2/3 diastolic blood pressure.

[h] Normal laboratory values: arterial pH, 7.35 to 7.45; Pao_2/Fio_2 ratio, greater than 300 mm Hg (normal oxygenation); $Paco_2$, 35 to 45 mm Hg; serum bicarbonate, 22 to 28 mEq/L; serum lactate, 0.5 to 2.0 mmol/L; serum sodium, 135 to 145 mEq/L; serum potassium, 3.5 to 5.0 mEq/L; serum chloride, 98 to 106 mEq/L; total serum calcium, 8.5 to 10.5 mg/dL; serum ionized calcium, 4.5 to 5.3 mg/dL; serum albumin, 3.5 to 5.0 g/dL; serum creatinine, 0.6 to 1.2 mg/dL; and blood urea nitrogen, 7 to 20 mg/dL.

analysis included 627 patients, comparing 314 in the bicarbonate group with 313 in the control group. **Table 1** presents the main patient characteristics.[26-28] The 2 groups were well balanced. The median pH at enrollment was 7.15 (IQR, 7.08-7.18) in the bicarbonate group and 7.15 (IQR, 7.09-7.19) in the control group, and the serum lactate level was greater than 2 mmol/L in 475 of 588 patients (81%). Other causes of metabolic acidosis are listed in eTable 11 in Supplement 1.

Intervention

Arterial pH, serum bicarbonate level, $Paco_2$, and creatinine level in the control and bicarbonate groups during the first 48 hours are reported in eFigures 2 through 6 in Supplement 1. Arterial pH, serum bicarbonate level, $Paco_2$, and serum creatinine level over time are displayed in eFigures 2 through 5 in Supplement 1. Patients in the bicarbonate group received a median of 750 mL (IQR, 500-1000 mL) of 4.2% sodium bicarbonate within the first 48 hours, with initiation 15 minutes (IQR, 6-36 minutes) after enrollment.

Outcomes

Primary Analysis

Day 90 all-cause mortality was 195 of 314 patients (62.1%) in the bicarbonate group and 193 of 313 (61.7%) in the control group (absolute difference, 0.4; 95% CI, −7.2 to 8.0; $P = .91$) (**Table 2**). Cumulative incidence of death within 90 days after enrollment was not different between the 2 groups (hazard ratio, 0.97; 95% CI, 0.80-1.19; $P = .78$) (**Figure 2**A). After adjustment for randomization strata (center, pH, and age), the results remained nonsignificant (eTable 2 in Supplement 1). Using inverse probability weighting to account for potential post-randomization selection bias, we found no evidence of a group effect on the primary outcome (odds ratio, 0.63; 95% CI, 0.33-1.15) (eTable 2 in Supplement 1). Similarly, no evidence of a group effect on the primary outcome was observed in the pre-planned subgroup analyses based on each randomization stratum or in the post hoc subgroup analyses (**Figure 3**).

Kidney replacement therapy use is reported in Table 2. The median time to KRT initiation was 31 hours (IQR, 12-70 hours)

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Table 2. Primary and Secondary Outcomes[a]

Outcomes	Group		Unadjusted absolute difference (95% CI)
	Bicarbonate (n = 314)	Control (n = 313)	
Primary outcome			
Day 90 all-cause mortality, No./total No. (%)	195/314 (62)	193/313 (62)	0.4 (−7.2 to 8.0)
Secondary outcomes			
Day 28 all-cause mortality, No./total No. (%)	171/314 (54)	170/313 (54)	0.2 (−7.7 to 7.9)
Day 180 all-cause mortality, No./total No. (%)	204/314 (65)	196/313 (63)	2.4 (−5.2 to 9.9)
Use of KRT by day 28, No./total No. (%)	109/314 (35)	157/313 (50)	−15.5 (−23.1 to −7.8)
KRT-free days by day 28, median (IQR)	0 (0 to 28)	0 (0 to 28)	0.0 (0.0 to 0.0)
KRT-free days by day 28 in survivors, median (IQR)	28 (26 to 28) [n = 143]	28 (23 to 28) [n = 143]	0.0 (0.0 to 0.0)
Enrollment to KRT initiation, median (IQR), h	30.9 (12.2 to 69.6) [n = 108]	15.5 (5.3 to 32.4) [n = 156]	13.0 (6.4 to 20.8)
Vasopressor therapy by day 28, No./total No. (%)	305/314 (97)	293/313 (94)	3.5 (0.3 to 6.8)
Vasopressor-free days by day 28, median (IQR)	0 (0 to 24)	0 (0 to 25)	0.0 (0.0 to 0.0)
Vasopressor-free days by day 28 in survivors, median (IQR)	25 (22 to 26) [n = 143]	25 (22 to 26) [n = 143]	0.0 (0.0 to 1.0)
Invasive MV by day 28, No./total (%)	287/314 (91)	275/313 (88)	3.5 (−1.2 to 8.3)
Invasive MV-free days by day 28, median (IQR)	0 (0 to 21) [n = 313]	0 (0 to 23) [n = 313]	0.0 (0.0 to 0.0)
Invasive MV-free days by day 28 in survivors, median (IQR)	22 (16 to 26) [n = 142]	25 (16 to 27) [n = 143]	-1.0 (-2.0 to 0.0)
ICU length of stay by day 28, median (IQR), d	5 (2 to 11)	5 (1 to 12)	0.0 (0.0 to 1.0)
ICU-free days by day 28, median (IQR)	0 (0 to 18)	0 (0 to 17)	0.0 (0.0 to 0.0)
ICU-free days by day 28 in survivors, median (IQR)	19 (8 to 23) [n = 143]	19 (4 to 23) [n = 143]	0.0 (−1.0 to 2.0)
Hospital length of stay by day 90, median (IQR), d	10 (2 to 28)	8 (1 to 26)	0.0 (0.0 to 1.0)
Hospital-free days by day 90, median (IQR)	0 (0 to 50)	0 (0 to 48)	0.0 (0.0 to 0.0)
Hospital-free days by day 90 in survivors, median (IQR)	60 (41 to 76) [n = 119]	62 (37 to 77) [n = 120]	0.0 (−4.0 to 6.0)
Day 1 SOFA score, median (IQR)[b]	10 (8 to 13) [n = 220]	11 (8 to 14) [n = 203]	0.0 (-1.0 to 0.0)
Day 2 SOFA score, median (IQR)[b]	10 (6 to 13) [n = 187]	10 (6 to 13) [n = 172]	0.0 (-1.0 to 1.0)
Day 7 SOFA score, median (IQR)[b]	7 (3 to 11) [n = 139]	6 (3 to 11) [n = 118]	0.0 (-1.0 to 1.0)
Day 2 fluid balance, median (IQR), mL[c]	2805 (750 to 5952) [n = 282]	2200 (0 to 4870) [n = 251]	954.0 (320.0 to 1615.0)
ICU-acquired infection, No./total No. (%)			
Any infection	61/314 (19)	64/313 (20)	−1.0 (−7.2 to 5.3)
Pneumonia	32 (10)	41 (13)	−2.9 (−8.0 to 2.1)
Catheter-related infection	15 (5)	12 (4)	1.0 (−2.2 to 4.1)
Bloodstream infection	14 (4)	28 (9)	−4.5 (−8.4 to −0.6)
Urinary tract infection	3 (1)	5 (2)	−0.6 (−2.4 to 1.1)

Abbreviations: ICU, intensive care unit; KRT, kidney replacement therapy; MV, mechanical ventilation; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.

[a] CIs of median difference were estimated by the Hodges-Lehmann method.

[b] The SOFA score[28] is computed as the sum of 6 subscores (cardiovascular, respiratory, neurologic, kidney, hepatic, and hematologic), each of which ranges from 0 to 4; the total score can thus range from 0 to 24, with higher values indicating greater severity of organ failure.

[c] Sodium bicarbonate infusion accounted for 750 mL (IQR, 500-1000 mL) in the sodium bicarbonate group and 0 mL (IQR, 0-0 mL) in the control group. See details of fluid therapy in eTable 6 in Supplement 1.

in the bicarbonate group vs 16 hours (IQR, 5-32 hours) in the control group. With sodium bicarbonate therapy, the hazard ratio for KRT initiation during the first 28 days was 0.59 (95% CI, 0.46-0.75) (Figure 2B). The main reasons for initiating KRT were persistent oliguria, refractory acidemia, and elevated serum creatinine or blood urea nitrogen level (eTable 5 in Supplement 1). Among the patients who received KRT, we found no evidence of a group effect on day 90 all-cause mortality (eFigure 7 in Supplement 1). The major adverse kidney events outcome was met on day 90 in 199 of 240 patients (83%)

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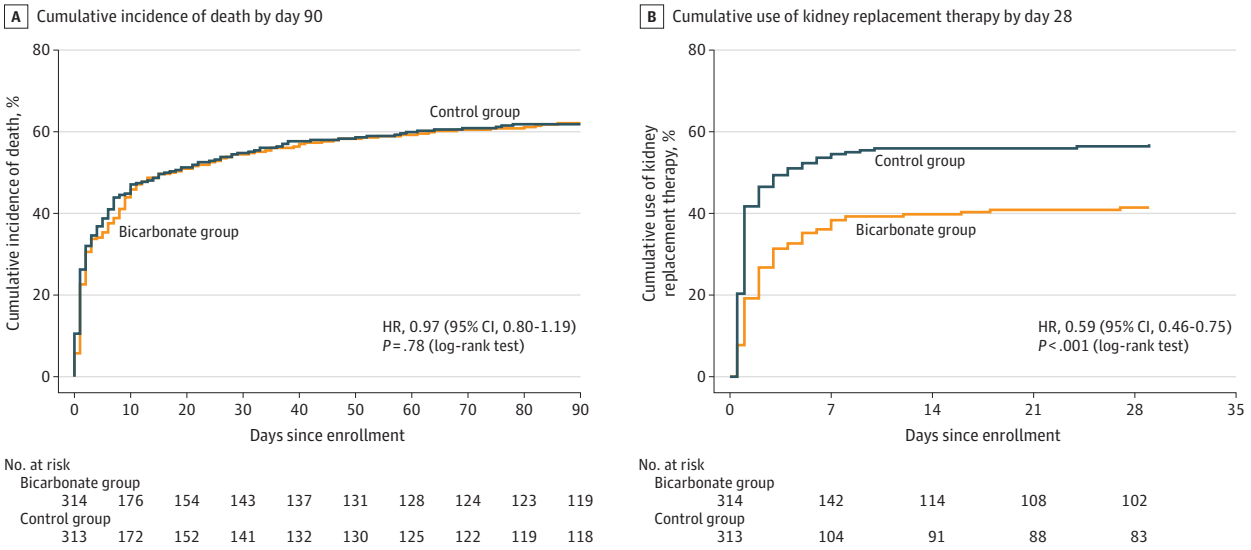
Figure 2. Cumulative Incidence of Death by Day 90 (Primary Outcome) and Cumulative Use of Kidney Replacement Therapy by Day 28 (Secondary Outcome)



A, Death was observed after 18 days (95% CI, 2-90 days) in the sodium bicarbonate group and 16 days (95% CI, 1-90 days) in the control group. B, Kidney replacement therapy was initiated 4.5 days (95% CI, 1-29 days) after enrollment for the bicarbonate group and 1 day (95% CI, 0.5-29 days) after enrollment for the control group. HR indicates hazard ratio.

in the bicarbonate group and in 195 of 232 controls (84%; absolute difference, −1.1; 95% CI, −7.8 to 5.6).

We found no evidence of a group effect on the use or duration of vasopressor therapy or invasive mechanical ventilation or on the length of ICU or hospital stay (Table 2). Bloodstream infections acquired in the ICU occurred in 28 of 313 controls (9%) and 14 of 314 patients (4%) in the bicarbonate group (Table 2). In addition, ICU-acquired bloodstream infections were observed in 26 of 266 patients (10%) who received KRT and 16 of 361 patients (4%) who did not. Table 2 reports the day 7 SOFA scores, and eTables 3, 4, and 6 in Supplement 1 show additional data on mortality in different types of metabolic acidosis and fluid therapy.

Per-Protocol Analysis

Although 578 of 627 patients (92%) received the treatment allocated by randomization (Figure 1), 47 patients in the control group received sodium bicarbonate (eTable 7 in Supplement 1), whereas 2 patients in the bicarbonate group did not. Baseline characteristics of the patients included in the per-protocol analysis are shown in eTable 8 in Supplement 1. The timing of sodium bicarbonate administration among these 47 patients according to day 90 all-cause mortality is shown in eFigure 8 in Supplement 1. We found no evidence of a group effect on day 90 all-cause mortality (eTable 9 in Supplement 1). Kidney replacement therapy was used for 118 of 252 patients (47%) who did not receive sodium bicarbonate and for 134 of 349 patients (38%) who did (eTable 9 in Supplement 1).

We found no evidence of a group effect on adverse events (eTable 10 in Supplement 1).

Discussion

In this multicenter randomized clinical trial of critically ill patients with severe metabolic acidemia and moderate to severe AKI, sodium bicarbonate therapy did not significantly reduce mortality within 90 days.

There was no evidence of a group effect on the primary outcome in the various post hoc subgroup analyses (Figure 3). However, patients in the bicarbonate group received KRT less often, and the proportion of patients with bloodstream infections was 50% lower in the bicarbonate group than in the control group. There was no evidence of group effect on the other secondary outcomes, including adverse events.

The findings differ from those of the BICARICU-1 trial.[3] Moderate to severe (stage 2 or 3) AKI was a randomization stratum and not an inclusion criterion in that trial and was present in only 47% of patients. A lower incidence of the primary composite outcome (day 28 mortality, at least 1 organ failure on day 7, or both) with sodium bicarbonate therapy was observed only in the prespecified stratum of patients with AKI. That day 90 all-cause mortality did not differ between groups in the present trial may be related to the design differences between the 2 trials. Moreover, that half the centers in the present trial did not participate in the BICARICU-1 trial[3] may also have contributed to the differences in the results. In the BICARICU-1 trial,[3] day 90 all-cause mortality was not the primary outcome and was collected as post hoc unpublished data. The post hoc analysis of data from the BICARICU-1 trial used to estimate the sample size for the present second trial predicted a day 90 mortality rate

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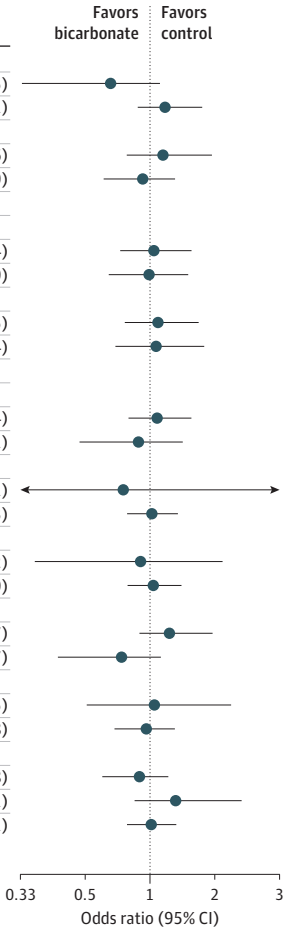
Figure 3. Plot of Day 90 Mortality Overall According to Randomization Strata for the Preplanned and Post Hoc Subgroups

Randomization strata	Death at 90 days (%) Bicarbonate group	Control group	Odds ratio (95% CI)
pH			
≤7.10	61/96 (64)	70/95 (74)	0.62 (0.34-1.15)
7.11-7.20	134/218 (61)	123/218 (56)	1.23 (0.84-1.81)
Age, y			
<65	77/132 (58)	70/130 (54)	1.20 (0.74-1.96)
≥65	118/182 (65)	123/183 (67)	0.90 (0.58-1.39)
Preplanned subgroups			
Sepsis			
Yes	106/172 (62)	100/166 (60)	1.06 (0.69-1.64)
No	89/142 (63)	92/146 (63)	0.99 (0.61-1.59)
Median SOFA score			
<11	85/166 (51)	71/147 (48)	1.12 (0.72-1.75)
≥11	106/142 (75)	113/155 (73)	1.09 (0.65-1.84)
Post hoc subgroups			
Type of admission			
Medical	136/214 (64)	132/216 (61)	1.11 (0.75-1.64)
Surgical	59/100 (59)	61/97 (63)	0.85 (0.48-1.51)
Cardiac arrest			
Yes	17/20 (85)	16/18 (89)	0.71 (0.10-4.81)
No	178/294 (61)	176/294 (60)	1.03 (0.74-1.43)
Hemorrhagic shock			
Yes	29/44 (66)	31/45 (69)	0.87 (0.36-2.12)
No	166/270 (61)	161/267 (60)	1.05 (0.74-1.49)
Kidney SOFA score			
≤2	132/200 (66)	112/187 (60)	1.30 (0.86-1.97)
≥3	63/114 (55)	80/125 (64)	0.70 (0.41-1.17)
Serum lactate, mg/dL			
≤18	23/52 (44)	26/61 (43)	1.07 (0.51-2.25)
>18	161/245 (66)	154/230 (67)	0.95 (0.65-1.38)
Centers participating in studies			
BICARICU-1 and BICARICU-2	125/206 (61)	131/204 (64)	0.86 (0.58-1.28)
BICARICU-2	70/108 (65)	62/109 (57)	1.40 (0.81-2.41)
Overall	195/314 (62)	193/313 (62)	1.02 (0.74-1.41)



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Interactions were tested between the treatment and each group, and none were significant. Kidney replacement therapy was initiated 4.5 days (95% CI, 1-29 days) in the bicarbonate group and 1 day (95% CI, 0.5-29 days) after enrollment in the control group. SOFA indicates Sequential [Sepsis-related] Organ Failure Assessment.

of 70% to 80%, whereas the observed day 90 all-cause mortality was 62%. In the BICARICU-2 trial, baseline pH, AKI severity, and day 2 fluid balance were within the ranges observed in the AKI stratum of patients in BICARICU-1 (Table 1).[3] However, KRT was used less often in BICARICU-2 than in the AKI stratum of BICARICU-1 (157 of 313 [50%] vs 66 of 90 [73%] controls and 109 of 314 [35%] vs 47 of 92 [51%] patients in the bicarbonate group; absolute difference, −15.5; 95% CI, −23.1 to −7.8) (Table 2, Figure 3). In addition, the median time to KRT initiation was longer in the present trial (16 hours [IQR, 5-32] vs 7 hours [IQR, 3-17] for controls and 31 hours [IQR, 12-70] vs 20 hours [IQR, 8-82] for the bicarbonate group). There was no evidence of a group effect on the proportion of patients with adverse events. Thus, sodium bicarbonate therapy as used in the present trial seems safe and may delay or avoid KRT for some patients. Oliguria and acidemia were less common reasons for KRT initiation in the bicarbonate group, possibly reflecting a higher physician threshold for initiating KRT according to these criteria (eTable 5 in Supplement 1). These findings align with timing trials[16-19] that have contributed to decreased KRT use in the ICU. Nevertheless, another plausible explanation for the divergent findings regarding mortality in patients with moderate to severe AKI is that large-effect estimates from smaller trials or subgroup analyses may occur by chance.[29]

Given that KRT is associated with adverse events and excess costs, using it only when necessary is desirable.[30,31] The observed 50% reduction in the proportion of patients with bloodstream infections in the bicarbonate group compared with controls may be related to decreased KRT use; however, this possibility remains speculative.

Sodium bicarbonate was administered to 47 patients randomly assigned to the control group. Day 90 all-cause mortality in these 47 patients was 72% compared with 62% in the controls and bicarbonate group. Kidney replacement therapy was used in 31 of 47 of these patients (66%) compared with 109 of 314 patients (35%) in the bicarbonate group. Thus, the administration of sodium bicarbonate seems to be a marker of disease severity and may be used as rescue therapy.

Limitations

First, a limitation of the trial is the open-label design. Although 1 blinded pilot trial has been published,[32] both the present study and the previously reported trial[32] allowed

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bedside clinicians access to blood gas measurements, which is clinically necessary, given the severity of the patients' condition. The MOSAICC trial is an ongoing open-label trial in the United Kingdom that will evaluate sodium bicarbonate infusion in critically ill patients presenting with moderate acidemia (pH <7.30) and moderate to severe AKI.[33] Second, the sodium bicarbonate dose was not computed according to laboratory tests or the weight of each patient but was instead individualized to target a pH of 7.30 or higher, with a maximum dose of 500 mEq of sodium bicarbonate during 24 hours. Third, 47 of 313 controls (15%) received sodium bicarbonate therapy. However, the per-protocol analysis that distinguished controls and bicarbonate patients according to the treatment administered, as opposed to the treatment assigned, showed no significant difference in day 90 all-cause mortality. Fourth, recommendations in both groups were made to initiate KRT if life-threatening hyperkalemia, acidemia, or overload criteria were met. Sodium bicarbonate infusion increases pH and may therefore have delayed KRT initiation in the bicarbonate group by lessening the influence of the acidemia criterion.

Conclusions

For critically ill patients who had both severe metabolic acidemia and moderate to severe AKI, sodium bicarbonate therapy did not significantly decrease day 90 all-cause mortality.

ARTICLE INFORMATION

Accepted for Publication: October 6, 2025.

Published Online: October 29, 2025. doi:10.1001/jama.2025.20231

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Obtained funding: Jung, Rieu.
Administrative, technical, or material support: Jung, Jabaudon, Canet, Jeantrelle, Pottecher, Garcon, Forel, Benchabane, Richard, Molinari, Jaber.
Supervision: Jung, Jabaudon, De Jong, Bitker, Klouche, Futier, Molinari, Jaber.
Enrolled patients: Reignier.

Conflict of Interest Disclosures: Dr De Jong reported consulting fees from Sanofi, Viatris, and Medtronic. Dr Bitker reported reimbursement of travel expenses related to attending scientific meetings from Pfizer. Dr Lasocki reported consulting fees from CSL Vifor and Pharmacosmos and speaking fees from CSL Vifor, Pharmacosmos, Masimo, and Pfizer. Dr Canet reported lecturer and speaker fees, as well as reimbursements of travel and accommodation expenses related to attending scientific meetings, from Gilead, Shionogi, and Sanofi Genzyme. Dr Corne reported reimbursement of travel expenses related to attending scientific meetings from Pfizer. Dr Benchabane reported reimbursement of travel expenses related to attending scientific meetings from AOP. Dr Richard reported reimbursement of travel expenses related to attending scientific meetings from Pfizer. Dr Jaber reported consulting fees from Dräger, Mindray, Medtronic, Baxter, Fresenius Xenios, and Fisher & Paykel. No other disclosures were reported.

Funding/Support: This trial was funded by the French Ministry of Health (Programme Hospitalier de Recherche Clinique National, 2018; 18-18-0328). The sponsor was the Montpellier University Hospital.

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Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The BICARICU-2 study investigators are listed in Supplement 5.

Data Sharing Statement: See Supplement 6.

Meeting Presentation: Presented at LIVES, the ESICM 38th Annual Congress; October 29, 2025; Munich, Germany.

Additional Contributions: We thank Aria Wolfe, MD, for her help editing the manuscript; and Peter Goldberg, MD, McGill University, for his advice and expertise.

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